

Claims

1. A recombinant antibody or an antibody fragment thereof wherein the recombinant antibody or the antibody fragment thereof specifically binds to human insulin-like growth factor-I (IGF-I) and human insulin-like growth factor-II (IGF-II) to inhibit the biological activities of human IGF-I and human IGF-II.

2. The recombinant antibody or the antibody fragment thereof according to (1) Claim 1, , wherein the recombinant antibody or the antibody fragment thereof binds to human IGF-I and human IGF-II at the same degree.

3. The recombinant antibody or the antibody fragment thereof according to Claim 1 or 2, wherein the recombinant antibody or the antibody fragment thereof has the binding activity with a binding constant of $5 \times 10^9 \text{ M}^{-1}$ or more measured with a biosensor BIACORE to human IGF-I and human IGF-II.

4. The recombinant antibody or the antibody fragment thereof according to any one of Claims 1 to 3, wherein the recombinant antibody or the antibody fragment thereof belongs to the IgG class

5. The recombinant antibody or the antibody fragment thereof according to any one of Claims 1 to 4, wherein the recombinant antibody comprises the complimentarity-determining regions (CDRs) of the heavy chain variable region (VH) and light chain variable region (VL) of a monoclonal antibody against human IGF.

6. The recombinant antibody or the antibody fragment thereof according to Claim 5, wherein the complimentarity-determining region (CDR)1, CDR2 and CDR3 of the VH of the recombinant antibody or the antibody fragment thereof are represented by SEQ ID NOS:5, 6 and 7, respectively.

7. The recombinant antibody or the antibody fragment thereof according to Claim 5, wherein the CDR1, CDR2 and CDR3 of the VL of the recombinant antibody or the antibody fragment thereof are represented by SEQ ID NOS:8, 9 and 10, respectively.

8. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 7, wherein the CDR1, CDR2 and CDR3 of the VH of the recombinant antibody or the antibody fragment thereof are represented by SEQ ID NOS:5, 6 and 7, respectively and the CDR1, CDR2 and CDR3 of the VL are represented by SEQ ID NOS:8, 9 and 10, respectively.

9. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 8, wherein the VH of the recombinant antibody or the antibody fragment thereof comprises an amino acid sequence in which at least one amino acid selected from 1st position Gln, 11th position Val, 42nd position Gly, 75th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:11 is substituted or an amino acid sequence in which at least one amino acid selected from 49th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:54 is substituted.

10. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 8, wherein the VL of the recombinant antibody or the antibody fragment thereof the antibody comprises an amino acid sequence in which at least one amino acid selected from 4th position Met, 9th position Asp, 10th position Ser, 11th position Leu, 15th position Leu, 22th position Asn, 35th position Tyr, 39th position Pro, 42th position Pro, 45th position Leu, 46th position Leu, 69th

position Asp, 70th position Phe, 71st position Thr, 82nd position Val, and 84th position Val in the amino acid sequence represented by SEQ ID NO:14 is substituted or an amino acid sequence in which at least one amino acid selected from 4th position Met, 9th position Ser, 10th position Ser, 11th position Leu, 15th position Val, 35th position Tyr, 39th position Pro, 42nd position Ala, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71th position Thr, and 82nd position Phe in the amino acid sequence represented by SEQ ID NO:55 is substituted.

11. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 10, wherein the VH of the recombinant antibody or the antibody fragment thereof comprises an amino acid sequence in which at least one amino acid selected from 1st position Gln, 11th position Val, 42th position Gly, 75th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:11 is substituted or an amino acid sequence in which at least one amino acid selected from 49th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:54 is substituted and the VL comprises an amino acid sequence in which at least one amino acid selected from 4th position Met, 9th position Asp, 10th position Ser, 11th position Leu, 15th position Leu, 22th position Asn, 35th position Tyr, 39th position Pro, 42th position Pro, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, 82nd position Val, and 84th position Val in the amino acid sequence represented by SEQ ID NO:14 is substituted or an amino acid sequence in which at least

one amino acid selected from 4th position Met, 9th position Ser, 10th position Ser, 11th position Leu, 15th position Val, 35th position Tyr, 39th position Pro, 42nd position Ala, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, and 82nd position Phe in the amino acid sequence represented by SEQ ID NO:55 is substituted.

12. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 11, wherein the VH of the recombinant antibody or the antibody fragment thereof comprises an amino acid sequence in which at least one amino acid selected from 1st position Gln, 11th position Val, 42nd position Gly, 75th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:11 is substituted and the VL comprises an amino acid sequence in which at least one amino acid selected from 4th position Met, 9th position Asp, 10th position Ser, 11th position Leu, 15th position Leu, 22nd position Asn, 35th position Tyr, 39th position Pro, 42nd position Pro, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, 82nd position Phe, and 84th position Val in the amino acid sequence represented by SEQ ID NO:14 is substituted.

13. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 11, wherein the VH of the recombinant antibody or the antibody fragment thereof comprises an amino acid sequence in which at least one amino acid selected from 49th position Ser, 77th position Asn, 84th position Asn, 93rd position Val, 97th position Ala, and 98th position Arg in the amino acid sequence represented by SEQ ID NO:54 is substituted and the VL comprises an amino acid sequence in which at least one amino acid selected from 4th position

Met, 9th position Ser, 10th position Ser, 11th position Leu, 15th position Val, 35th position Tyr, 39th position Pro, 42th position Ala, 45th position Leu, 46th position Leu, 69th position Asp, 70th position Phe, 71st position Thr, and 82nd position Phe in the amino acid sequence represented by SEQ ID NO:55 is substituted.

14. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 8 or 12, wherein the VH of the recombinant antibody or the antibody fragment thereof comprises an amino acid sequence represented by SEQ ID NO:26.

15. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 8 or 12, wherein the VL of the recombinant antibody or the antibody fragment thereof comprises an amino acid sequence represented by SEQ ID NO:27, 28 or 29.

16. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 8, 12, 14 or 15, wherein the VH of the recombinant antibody or the antibody fragment thereof comprises an amino acid sequence represented by SEQ ID NO:26 and the VL comprises an amino acid sequence represented by SEQ ID NO:27, 28 or 29.

17. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 8, 12, 14 to 16, wherein the VH of the recombinant antibody or the antibody fragment thereof comprises an amino acid sequence represented by SEQ ID NO:26 and the VL comprises an amino acid sequence represented by SEQ ID NO:27.

18. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 8, 12, 14 to 16, wherein the VH of the recombinant antibody or the antibody

fragment thereof comprises an amino acid sequence represented by SEQ ID NO:26 and the VL comprises an amino acid sequence represented by SEQ ID NO:28.

19. The recombinant antibody or the antibody fragment thereof according to any one of Claims 5 to 8, 12, 14 to 16, wherein the VH of the recombinant antibody or the antibody fragment thereof comprises an amino acid sequence represented by SEQ ID NO:26 and the VL comprises an amino acid sequence represented by SEQ ID NO:29.

20. The recombinant antibody or the antibody fragment thereof according to any one of Claims 1 to 19, wherein the recombinant antibody is a human CDR-grafted antibody.

21. The recombinant antibody or the antibody fragment thereof according to any one of Claims 1 to 19, wherein the antibody fragment is an antibody fragment selected from Fab, Fab', F(ab')₂, single-stranded antibody (scFv), dimerized variable region (diabody), disulfide-stabilized variable region (dsFv), and CDR-containing peptide.

22. DNA encoding the recombinant antibody or the antibody fragment thereof according to any one of Claims 1 to 21.

23. An expression vector carrying DNA according to Claim 22.

24. A transformant obtained by introducing the expression vector according to Claim 23.

25. A process for producing a recombinant antibody or the antibody fragment thereof, which comprises a step of culturing the transformant according to Claim 24 in a medium to produce and accumulate the recombinant antibody or the antibody fragment thereof according to any one of Claims 1 to 21 in a culture, and isolating and purifying the recombinant

antibody or the antibody fragment thereof from the culture.

26. A medicament which comprises the recombinant antibody or the antibody fragment thereof according to any one of Claims 1 to 21 as an active ingredient.

27. A therapeutic agent for IGF-associated diseases, which comprises the recombinant antibody or the antibody fragment thereof according to Claims 1 to 21.

28. A therapeutic agent according to Claim 27, wherein the IGF-associated diseases are cancer, acromegaly and diabetic complications.